Primary progressive multifocal leukoencephalopathy: report of a case

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Summary

The authors describe a case of primary progressive multifocal leukoencephalopathy (pPML). Unlike previous similar reports, our patient underwent up-to-date and extensive in vivo and post-mortem investigations that established beyond doubt the competence of his immune system and the absence of underlying predisposing disorders. The various implications of this case, both clinical and related to the possible pathogenetic mechanisms of JC virus infection, are discussed.

KEY WORDS: immunocompetence, JC, PML.

Introduction

Progressive multifocal leukoencephalopathy (PML) is an infrequent central nervous system demyelinating disorder due to the polyomavirus JC (JCV). Anti-JCV antibodies are detectable in 75% of the general adult population, but the disease usually develops as a result of a reactivation of a latent form of the virus in the presence of a primary (i.e., acquired immunodeficiency syndrome, AIDS) or secondary (to severely debilitating illness) disorder of the immune system (1).

However, PML has, on rare occasions, also been observed in subjects with no underlying predisposing disorders, i.e., as a primary condition (pPML) (2). Most reports of pPML lack appropriate in vivo investigations of patients’ immunological status: the earliest ones date back to times when modern diagnostic techniques were not available (3-11), whereas more recent ones have concerned cases diagnosed after the patient’s death (3-5,12-16).

We report the case of a patient diagnosed with pPML during life on clinical and microbiological grounds (the diagnosis was subsequently confirmed at autopsy). Extensive laboratory investigation had established beyond doubt the competence of this patient’s immune system.

Case report

The patient, a 65-year-old man, was a retired clerk. He reported a past history of chronic gastritis and hiatal hernia, and he had undergone inguinal hernia repair at age 44. He had also suffered an asymptomatic myocardial infarction one year before admission to our department, followed by aorto-coronaric bypass surgery. In October 1999 the patient was admitted to a neurology unit because of fluctuating headache and personality changes (characterized by alternate euphoric and depressed mood) that had appeared about one month earlier. The neurological examination was unremarkable. A brain computed tomography (CT) scan revealed a hypodense, non enhancing lesion in the subcortical white matter of the anterior part of the right frontal lobe. At discharge, 10 days later, the clinical picture was stable and the diagnosis was “frontal syndrome of probable vascular origin”.

Over the following weeks, the patient experienced a gradual onset of gait difficulties and progressive psychomotor slowing and, in the December, he was admitted to our hospital.

General physical examination was within normal limits. At the neurological examination, mental status appeared to be normal, except for slowing of thought and speech and mild dysphoria. The palmomental reflex was positive on the left. The cranial nerves were intact. Motor examination showed moderate strength decrease and slight increase of muscular tone and deep tendon reflexes in the left arm and leg; Babinski sign was also present on the left. Pinprick sense was impaired in the left hemi-body. Neither ataxia nor dysmetria were present on finger-to-nose and heel-to-shin testing. The patient showed a left hemiparetic gait with mild left foot drop.

Routine laboratory investigations were unremarkable (complete and differential blood cell count, haemoglobin, serum protein electrophoresis, serum electrolytes, calcium, urea nitrogen, uric acid, creatinine, bilirubin, hepatic enzymes, fasting blood glucose, cholesterol and triglycerides, amylaseaemia, sedimentation rate, C-reactive protein, creatine phosphokinase, coagulation, sideraemia, routine urinanalysis). Bence-Jones proteinuria was absent.
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Chest X-ray was also normal. An electrocardiogram showed signs of the previous left ventricular infarction. Electroencephalographic recording revealed bilateral dysrhythmia, more prominent in the right hemisphere. Brain CT scan performed at admission revealed enlargement of the previously reported right frontal white matter hypodensity; in addition, two similar, newly-formed lesions in the left frontal and right parietal lobes were now apparent. None of these lesions showed either mass effect or enhancement after injection of iodine contrast. One week later, T2-weighted magnetic resonance imaging (Fig. 1) showed widespread hyperintensity in the centrum semiovale, most prominent in the right frontal white matter, in the anterior part of the corpus callosum, and at the level of the right internal and external capsules. Moderate mass effect was now present, with compression of the right frontal cortical sulci and right frontal horn. There was no enhancement after gadolinium.

A slightly traumatic lumbar puncture yielded clear cerebrospinal fluid under normal pressure, with 36 mg/dL proteins, 90 mg/dL glucose, 2 leukocytes/mmc and 66 red cells/mmc. Cytology confirmed the presence of red cells and lymphocytes and showed no malignant cells. Immunoelectrophoresis showed an IgG index of 0.45 (normal range: 0.4-0.6). Oligoclonal bands were absent. Microbiological studies were negative, with the exception of PCR analysis for JCV DNA, which was positive. DNA was detected by nested PCR amplification of the JCV T antigen region using positive (virus-transfected cells) and negative (samples amplified in the absence of template DNA) controls. Restriction enzyme BamH-1 was used to differentiate JCV DNA from SV40 and BK DNAs.

Clinical, neuroradiological and microbiological findings all strongly supported a diagnosis of PML and were considered sufficient diagnostic criteria (2), so brain biopsy was not performed.

Intravenous treatment with cidofovir was undertaken (5 mg/kg body weight once weekly for the first two weeks and then every two weeks thereafter, together with probenecid) and well tolerated. Over the following weeks no substantial clinical or neuroradiological improvement was observed and the patient gradually developed global aphasia and spastic tetraparesis. After about two months of treatment with cidofovir, intramuscular injections of beta-interferon (16 MIU daily) were added. However, the patient further deteriorated and progressed to coma, giving only intermittent responses to verbal and noxious stimuli. Tracheostomy and percutaneous gastrostomy had to be performed because of impairment of swallowing and of autonomous respiration.

Neuroimaging monitoring showed progressive enlargement and confluence of the white-matter lesions and a moderate mass effect with compression of ventricles and cortical sulci. Contrast medium injection was not performed. The last CT scan, dated the end of April 2000, showed widespread subcortical hypointensity and marked cerebral atrophy.

After clinical and microbiological diagnosis was reached, an extensive laboratory search for putative underlying malignancy, coinfections and immunodepression was performed. Serology for HIV, carried out about three months after disease onset, was negative and remained negative in two subsequent tests performed two and seven weeks later. Serology for syphilis (VDRL and TPHA) was non-reactive. Serology for cytomegalovirus was positive for IgG, but not for IgM, indicating a remote contact. Hepatitis B virus (HBV) antigens and antibodies as well as HCV and HAV antibodies were absent. Purified protein derivative skin testing was negative. Serology for Mycoplasma pneumoniae and Legionella pneumophila also continued to give negative findings during repeated bronchopneumonia episodes. Several neoplastic markers (PSA, CA 19-9, CEA, alpha-fetoprotein, beta HCG and CA 125) were searched twice during the patient’s hospital stay and were found to be within normal limits on both occasions.

Immune status was assessed by investigating complement and both humoral and cell-mediated immunity. Total leukocyte count was 5.7 M/mmc (normal range: 4.0-10.0), with 1.6 M lymphocytes/mmc (normal range: 1.5-4.0). A phenotypic study of the lymphocytic population revealed that 6% was CD20 positive (B cells) and 76% CD3 positive (T cells) (normal range: 5-15% and 66-80% respectively); the ratio of CD4/CD8 lymphocytes was 1.88 (normal range: 1.2-2.6). Serum levels of the main classes of immunoglobulins (IgM, IgG and IgA) were within normal limits. C4 complement component was normal, whereas C3 was slightly elevated (151, normal range: 75-140). Autoantibodies were absent.

Eleven months after disease onset, the patient lay in a vegetative, cachectic state. In July 2000, he died of cardio-respiratory complications of confluent bronchopneumonia.

On the following day, a general autopsy was performed; the patient’s brain was fixed in formalin and examined 40 days later.
Primary PML

Autopsy findings

*General* thoracic exploration revealed bilateral confluent bronchopneumonia, partial necrosis of the left ventricle and coronary bypass graft. All internal organs appeared rather atrophic but presented no evidence of malignancy or infection. *Brain* macroscopic examination showed severe gyral and periventricular atrophy, most prominent in the frontal and parietal lobes. Marked loss of white matter and multiple confluent foci of demyelination were found in both hemispheres. A cavitary lesion within a large demyelinated area was located in the right temporal lobe. No pathologic changes were detectable in the brainstem and cerebellum, except for widespread oedema. Microscopic examination revealed enlarged and bizarre astrocytes and swollen oligodendrocytes along the borders of demyelination. Reactive gliosis and chronic inflammatory, mainly perivascular, infiltrates (including lymphocytes and monocytes) were found in the white matter of the parietal, temporal and occipital lobes. Examination by electron microscopy showed the presence of numerous intranuclear particles, whose ultrastructural appearance was compatible with that of the polyomavirus.

Discussion

In this report we present the results of the extensive *in vivo* and post-mortem investigations performed in a case of pPML. This case report, as well as previous descriptions of pPML, has one main clinical implication: even though this is a very rare condition, immunocompetence should not be regarded as an exclusion criterion for diagnosis of PML. Moreover, these cases raise important questions about the pathogenetic mechanisms of JCV infection and reactivation. Perivascular lymphocyte cuffs and plasma cell infiltrates in brain tissue seem to be peculiar features of pPML (reflecting the efficiency of the immune response) (17) and were observed in our patient as well. These neuropathological findings apart, cases of pPML do not seem to share other distinctive demographic, neurological, laboratory or neuroradiological features distinguishing them from classic PML. Age at onset varies and ranges from youth to advanced old age. Clinical presentation is heterogeneous and shows no peculiarity with respect to PML associated with immunodeficiency: it may take the form of hemiparesis (5,12,13,18-20), cognitive decline (3,5,10,13,14,16,18), ataxia (4,16,20), visual deficits (4,5,10) or personality changes (as in the present case) (3,4,13); an extrapyramidal syndrome (14) or recurrent epileptic seizures (5) are additional, more unusual manifestations. Prolonged survival is more frequently reported in immunocompromised than in immunocompromised patients; but this does not appear to be a constant or exclusive feature of primary cases. Differences in the virulence of different JCV variants (6,21) and in patients’ individual immunoreactivity are more crucial determinants of variability of clinical evolution. Neuroimaging findings do not differ from the neuroradiological picture “classically” observed in PML. The mass effect observed in our patient is actually an infrequent finding, but does not seem to relate to the primary nature of the disease, having also been detected in some AIDS-associated PML cases (22,23). Cerebrospinal fluid may show only minor elevations in cell count and protein content. EEG findings are usually abnormal, but totally aspecific. The medical history of pPML patients (considering cases in which it was adequately investigated and described) appears extremely various. Some reported associations, such as those with haemochromatosis (13) or congestive cardiopathy (16), appear spurious and do not really suggest a causal relationship. More convincing evidence supports a possible predisposing role for other past or concomitant medical events: active hepatitis C and anti-DNA antibody positivity (18), cerebral toxoplasmosis (15), alcohol abuse (13).

As regards our patient’s medical history, six months before neurological referral he had undergone coronary bypass surgery. Surgical procedures have been shown to induce a transient (few days’) decrease in circulating T-lymphocyte subpopulations (24): we speculate that reactivation of latent JCV may have occurred during an undetected transient postoperative immunological deficit, in a particularly vulnerable individual. Richardson stated that “only under conditions of chronic immunosuppression does it [the virus] become pathogenic” (25); however, the putative involvement of a temporary, but sufficiently severe immunodepressive state has otherwise been proposed for pPML. Rosas and co-workers (20), for instance, propose a predisposing role for pregnancy-associated immunological deficits in their case of pPML in a pregnant woman.

The hypothesis of a transient immunological deficit is, however, highly speculative and might even be at odds with evidence gathered in favour of an efficient immune response in pPML. An alternative, more convincing explanation advanced for the earliest cases of pPML (4,5) was that JCV might not necessarily be opportunistic in nature. However, this theory can be considered overcome by the subsequent demonstration that, despite the ubiquitousness of the virus, cases of PML are quite rare. The hypothesis of a rare, non opportunistic variant of JCV might perhaps seem more plausible: such a variant might be sufficiently virulent to overcome an efficient immune defence and thus infect and immediately determine the development of the disease in healthy subjects. However, the result of a histological study by Houff et al. in a biopsy-proven case of pPML argues against this hypothesis as well: in that case the authors were able to demonstrate the presence of JCV in the bone marrow, strongly suggesting that the infection spreads to the CNS by means of infected lymphocytes, likely after an asymptomatic period of latency (19). More microbiological studies are certainly needed to clarify these issues and further descriptions of cases of pPML might also make a further contribution.

References